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(71) Applicant: FISONS plc, Fison House Princes Street, Ipswich Suffolk IP1 1QH (GB)

(72) Inventor: Alsop, Ranulph Michael, 28 Windemere Drive, Alderley Edge Cheshire (GB)
Inventor: Milner, Jeremiah, 22 Albert Road, Cheltenham Gloucestershire (GB)

(74) Representative: Craig, Christopher Bradberry et al, Fisons plc 12 Derby Road, Loughborough Leicestershire LE11 0BB (GB)

(54) Oral compositions containing dextran.

(57) There is described a formulation, suitable for enteral administration to man, comprising a bulking proportion of a dextran having an average molecular weight of from 10,000 to 50,000,000.

There is also described a method of controlling the calorie intake of a human, of providing a bulking agent for a human or of treatment of a condition of the gastrointestinal tract in a human, which comprises administering enterally a composition containing a dextran of average molecular weight of from 10,000 to 50,000,000 to the appropriate human.

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ORAL COMPOSITIONS CONTAINING DEXTRAN

This invention relates to a new formulation and a method for its preparation.

Dextrans of a wide variety of molecular weights have been known for many years and certain dextrans, e.g. those having molecular weights of about 40,000 or 70,000, have found use in medicine for administration, by infusion, as blood plasma expanders. Certain dextrans have also, in some countries, been permitted as food additives and indeed native dextrans are sometimes present in small quantities in food grade sucrose. Bloom et al Proc Soc Exp Biol Med (1952) 81, 501 have shown that certain dextrans when ingested by man produce a rapid increase in blood sugar and liver glycogen. Furthermore digestibility and caloric availability assays in the rat have indicated that dextran is highly digestible.

A number of liquid formulations for the enteral feeding of patients are available. These are designed either to be swallowed or to be administered to the stomach, eg of an unconscious patient, by means of a tube. These liquids usually contain a balanced foodstuff and/or appropriate minerals and vitamins. However, these formulations seldom if ever contain much material which is not absorbed on the passage through the gastrointestinal tract. In consequence if the liquid feed is used for a

protracted period normal intestinal motility can be impaired and the patient can become severely constipated.

There is also a need for a water soluble bulking agent, which does not produce a surge of blood sugar, and which preferably yields no, or a small number of, calories, when introduced into the gastrointestinal tract. Such a bulking agent would be of use in compositions to be administered to diabetics, the obese or others where it is desired to control the calorie intake and minimise increases in blood sugar levels after administration of food. There is a still further need for a water soluble hydrophyllic bulking agent, which is substantially unabsorbed by the small intestine, for use in the treatment of conditions of the lower bowel.

Surprisingly, and contrary to the teaching of the art, we have found that certain dextrans do not produce any large or immediate increase in blood sugar and are not absorbed to an appreciable extent by man when administered enterally. Furthermore, in contrast to other carbohydrates (e.g. glucose or dextrin), these dextrans do not produce a substantial rise in blood insulin after ingestion. We have also surprisingly found that certain dextrans can reduce the asborption of other carbohydrates, e.g. glucose. These dextrans are therefore indicated for use as an essentially non-absorbed pharmaceutical or

foodstuff excipient.

According to the invention we provide a formulation, suitable for enteral administration to man, comprising a bulking proportion of a dextran having an average molecular weight of from 10,000 to 50,000,000.

According to the invention we also provide a method of controlling the calorie intake of a human, of providing a bulking agent for a human or of treatment of a condition of the gastrointestinal tract in a human, which comprises administering enterally a composition containing a dextran of average molecular weight of from 10,000 to 50,000,000 to the appropriate human.

The invention also provides a method of producing a formulation suitable for controlling the calorie intake of a human, for providing a bulking agent for a human or for the treatment of a condition of the gastro-intestinal tract, which comprises incorporating a dextran of average molecular weight of from 10,000 to 50,000,000 into an appropriate formulation.

The compositions are indicated for use in the treatment of, or as an adjunct in the treatment of, conditions of the lower gastrointestinal tract, eg Crohn's disease, ulcerative colitis, proctitis, coeliac disease regional ileitis, irritable bowel syndrome and the like. The compositions are also indicated for use in controlling

the blood glucose levels of diabetics and/or controlling calorie intake in those who are overweight or obese. The compositions are further indicated for conditions where a bulking agent is required, e.g. to promote the flow of material through the gastro-intestinal tract.

We prefer the composition to contain up to 30%, preferably up to 25%, e.g. up to 10%, w/w of the dextran. The composition also preferably contains more than 0.5% and preferably more than 2%, w/w of the dextran.

The dextran preferably has an average molecular weight of greater than 50,000, more preferably of greater than 200,000, and especially of about 250,000. The dextran preferably has an average molecular weight of less than about 1,000,000 and preferably less than 400,000. By dextran we mean a poly-glucose in which the glucose units are predominantly (e.g. 90% or more) linked in an alpha 1,6-configuration. Dextrans can be made by the action of the dextransucrase family of enzymes on sucrose. Dextransucrases are produced by various species of lactobacillae. We particularly prefer dextrans produced by Leuconostoc mesenteroides (and especially strain NRRL B512F). The dextrans produced by the action of the enzymes on sucrose are generally of very high molecular weight and may be partially hydrolysed and the hydrolysate fractionated to produce fractions of relatively narrow

bands of lower molecular weight. We prefer to use these fractionated dextrans. These dextrans are generally available in commerce and are of the same general type as, but are usually of a higher molecular weight than, the dextrans which are currently used for intravenous administration.

The dextran may be used in any suitable form, but is preferably incorporated in a foodstuff. The foodstuff is preferably a liquid, but may also be solid, e.g. a baked product such as bread or biscuits.

In liquids we have found that dextrans provide a useful thickening effect and also produce a pleasant and acceptable 'mouth feel'. The dextrans also provide a feeling of bulk in the stomach and can help prevent constipation in patients who are fed wholly or largely on liquids, or who are subject to dietary constraints because of conditions of the large intestine or bowel.

We prefer liquid formulations to contain from 0.5 to 7.0% w/w, e.g. about 2.25% w/w, of the dextran.

The liquid formulation may also contain other ingredients, such as flavours, e.g. fruit flavour; acids, e.g. phosphoric, citric, maleic, fumaric or tartaric acids; buffering agents, e.g. phosphates; sugars, e.g. fructose, sorbitol or sucrose. When the composition is to be used for a diabetic or for someone obese the calorie

content should be controlled, and preferably low. However when the composition is to be used for a patient, who may be unconscious, eg after surgery or a stroke, special balanced nutrients may be required. Thus the compositions may contain appropriate proportions of fats, carbohydrates, proteins, minerals and vitamins. The appropriate proportions of these nutrients are well known in the art. Specifically we provide the incorporation of the dextrans of the invention into existing commercially available foodstuff formulations, particularly liquid formulations designed for administration to those who are ill or obese, e.g. those sold under the Trade Marks "Ensure" and "Osmolite".

Any sweet taste in the composition may be provided by known natural or artificial sweeteners, e.g. saccharin, aspartame or cyclamates. The presence of the dextran in the formulation can help to mask or modify the unpleasant after-taste which is present with some artificial sweeteners.

The flavours may be provided in the form of fruit syrups or concentrates or by means of artificial flavours.

The compositions may, if desired (but preferably do not), contain other permitted food additives, e.g. gums, stabilisers, flavour boosters, preservatives (eg sodium benzoate) and/or anti-oxidants.

When the composition is designed to be administered by tube, eg a nasogastric tube, it is of course desirable that it be of such a viscosity that it can be readily passed through such a tube. In general the higher the molecular weight of the dextran the greater will be both the viscosity and the osmotic effect of the product.

The compositions may be made simply by mixing the ingredients in any convenient order. The mixture may then be filled into suitable containers, e.g. 100 to 500ml cartons or bottles, which may be pasturised or sterilised depending on the heat stability of the various components.

The dextrans have considerable hydrogen bonding ability and are heavily hydrated in the gastrointesinal tract. Thus the presence of the dextran in the compositions according to the invention can cause an increase in the water content of, and hence the general flow of material through, the gastrointestinal tract. The dextrans also have some anti-bacterial action and/or promote a favourable balance of bacteria in the gut. The compositions also help the flow of potentially toxic or allergic substances such as gluten peptides, enabling these to pass through the gut before they are absorbed.

The invention is illustrated, but in no way limited, by the following Examples.

Example 1 (Diabetic drink)

Dextran average molecular weight 500,000	2.5g
Fructose	5.0g
Citric acid anhydrous	0.125g
Blackcurrant concentrate	1.12ml
Distilled water	to 100ml

Example 2 (Nutrient formulation)

Protein	37 g/l
Carbohydrate (other than dextran)	145 g/l
Fat	37 g/l
Electrolytes, sodium, potassium and chloride	qs
Vitamins and minerals	qs
Dextran average molecular weight 500,000	25 g/l

Example 3

A liquid preparation is as follows:

Dextran m/w 250,000	5%	w/w
Sod. Benzoate	0.14%	"
Citric Acid	0.4%	"
Orange Flavour	0.3%	"
Sunset Yellow	0.08%	"
Saccharin Sodium	0.1%	"

Alternative sweeteners (Thaumatin, Aspartame etc) and flavours may be employed.

Example 4

Four consenting adult human volunteers were, on

separate occasions, given 50g each of glucose, sucrose, "Caloreen" (a polyglucose) and a dextran of average molecular weight 500,000 by mouth. The blood sugar and insulin levels of the volunteers were followed over a period of four hours after each administration. It was found that the blood sugar and insulin levels were considerably lower after the administration of the dextran than after the administration of the other materials.

Example 5

Ten consenting adult human volunteers were, after fasting and on separate occasions, given 50g each of glucose and "Caloreen" (a polyglucose produced by the methods described in US Patent No 3,928,135) by mouth. The volunteer's serum glucose and serum insulin levels were measured at various times. The results are shown in Tables I and II.

Fourteen consenting adult human volunteers were, after fasting, given 50g each of, in centre A, dextran of m/w 70,000 and, in centre B, dextran of m/w 250,000. The serum glucose and serum insulin levels, which are shown in Table III, show much lower increases than those in Tables I and II.

Table I Mean of 10 Volunteers after 50g Glucose

	Serum Glucose	Serum Insulin

Time (Mins)	Serum Glucose levels % increase	Serum Insulin levels % increase
0	100	100
30	168	710
60	141	610
90	120	580
120	97	280
150	94	210

Table II Mean of 10 Volunteers after 50g Polyglucose

Time (Mins)	Serum Glucose levels % increase	Serum Insulin levels % increase
0	100	100
30	165	730
60	140	590
90	110	410
120	106	340
150	100	220

Table III Mean of Two Groups of 8 & 6 Volunteers after 50g Dextran

Time (Mins)	Serum Glucose Levels % increase		Serum Insulin Levels levels	
	A	B	A	B
0	100	100	-	100
30	119	116	-	205
60	115	120	-	205
90	109	113	-	125
120	109	106	-	125
150	100	96	-	
180	94	-		
210	97	-		
240	97	-		
270	95	-		
300	96			

Example 6

In two of the volunteers in Centre A samples of serum were analysed (after removal of protein) by size exclusion chromatography. This technique is capable of determining amounts of oligosaccharides and simple sugars in the sample undergoing analysis. Table IV shows the % composition of serum carbohydrate in the two volunteers at various times after administration of the 50g dextran, compared with the dextran starting material.

It can be seen that there is no significant increase in serum carbohydrate during the test period other than glucose and that no oligosaccharides were absorbed.

Table IV Serum Carbohydrate Composition (%)

After 50g Dextran

Polymer Degree of Polymerisation	Volunteer SA Time (Secs) 0	60	300	Volunteer GG Time (Secs) 0	60	300	Dextran Administered
1(glucose)	88.3	94.2	92.6	88.1	93.4	92.7	1.3
2(isomaltose))	)		)		)	)	)
3	)		)	1.0	)	)	)
4	)			1.5	)	)	)
5	)		)		)	)	)
6	)		)	0.5	)	)	)
7	) 3.8	1.3	2.1	0.8	)1.3	)1.3	)2.7
8	)		)		)	)	)
9	)		)	2.1	)	)	)
10	)		)		)	)	)
11	)		)		)	)	)
12	)		)		)	)	)
Intermediate Mol. Wt.	1.6	0	0.6	1.1	0	0	8.1
High Mol. Wt.	6.4	4.5	4.7	5.0	5.5	7.1	87.9
Conc. Mg/ml	0.99	1.1	0.63	0.88	0.99	0.78	

Example 7

In a further experiment dextran m/w 250,000 was incubated for two hours at 37°C with artificial gastric juice. Analysis by size exclusion chromatography failed to detect any glucose in the product after this time.

Example 8

A human volunteer fitted with an ileostomy bag was administered 50g of dextran orally. The subject did no have a large intestine and the action of the normal digestive enzymes could therefore be studied in vivo. The subject was fasted overnight and at 0 time given 300 water containing 50g dextran m/w 70,000 and a radio labelled polyethylene glycol (PEG). Water was given during the succeeding five hours. All ileostomy fluid was collected and analysed for dextran and PEG content a for dextran molecular weight distribution. The recoveries of dextran and PEG are shown in Table V. Al dextran samples collected had the same molecular weight distribution as the starting material indicating that no hydrolysis of the dextran polymer had taken place. The recovery of the dextran matched closely that of the indigestible and non-absorbed polymer PEG showing that little, if any, absorption of dextran or dextran hydrolysis products had taken place.

Table V Dextran and PEG Recovery in Ileostomy Patient

Time	Dextran in Ileostomy Bag g	Dextran in Ileostomy Bag % Recovery	PEG in Ileostomy Bag % Recovery
0	-		
60	0.95	1.9	0
120	0.13	0.3	0.08
180	0.33	0.7	0.21
240	4.21	8.4	6.49
300	15.50	31.0	47.30
	21.10	42.3	54.08

Example 9

Two volunteers were on separate occasions administered 50g dextran m/w 70,000, 50g glucose and 50g dextran + 50g glucose orally in a standard glucose tolerance test procedure. The average % increase in serum glucose levels against time are shown in Table VI for the three experiments and compared with the calculated rise from the sum of the separate glucose and dextran data. It can be seen that the administration of 50g glucose together with 50g dextran gives lower serum glucose levels than 50g glucose alone and appreciably less than the calculated levels for the combined product.

Table VI Reduction of Glucose Asborption by Dextran

Time (Mins)	% Increase in Serum Glucose Levels			
	Glucose	Dextran	Glucose + Dextran	Glucose + Dextran (calc)
0	100	100	100	100
30	161	111	136	172
60	151	119	142	170
90	112	110	93	122
120	103	99	84	-
150	97	95	86	-
180	98	95	87	-

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What we claim is:-

1. A formulation, suitable for enteral administration to man, comprising a bulking proportion of a dextran having an average molecular weight of from 10,000 to 50,000,000.

2. A method of producing a formulation suitable for controlling the calorie intake of a human, for providing a bulking agent for a human or for the treatment of a condition of the gastro-intestinal tract, which comprises incorporating a dextran of average molecular weight of from 10,000 to 50,000,000 into an appropriate formulation.

3. A formulation or method according to Claim 1 or 2, wherein the formulation contains from 0.5 to 30% w/w of dextran.

4. A formulation or method according to Claim 3, wherein the formulation is liquid and contains from 0.5 to 7.0% w/w of dextran.

5. A formulation or method according to any one of the preceding claims, wherein the dextran has an average molecular weight of from 50,000 to 1,000,000.

6. A formulation or method according to Claim 5, wherein the dextran has an average molecular weight of 50,000 to 400,000.

7. A formulation or method according to any one of the preceding claims, wherein the dextran has been produced by Leuconostoc mesenteroides.

8. A formulation or method according to any one of the preceding claims, wherein the dextran is incorporated in a foodstuff.

9. A formulation or method according to Claim 8, wherein the foodstuff is a low calorie foodstuff.

10. A formulation or method according to any one of the preceding claims, wherein the formulation is a liquid suitable for administration by a nasogastric tube.

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